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reading frame of a *Saccharomyces cerevisiae* genome, wherein the *Saccharomyces cerevisiae* genome is shown in SEQ ID NOS:12,204-12,219, wherein the open reading frame is selected from the group consisting of the open reading frames identified by the SAGE tags shown in SEQ ID NO:67 (NORF 1), SEQ ID NO:68 (NORF 2), SEQ ID NO: 70 (NORF 4), SEQ ID NO: 71 (NORF 5), SEQ ID NO: 72 (NORF 6), SEQ ID NO: 83 (NORF 17), SEQ ID NO:91 (NORF 25), and SEQ ID NO:93 (NORF 27).

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43. (Twice Amended) The array of claim 32 which comprises at least one probe comprising at least 14 contiguous nucleotides of each of the open reading frames identified by the SAGE tags shown in SEQ ID NOS:67, 68, 70, 71, 72, 83, 91, and 93.

REMARKS

The Amendments

Claim 32 has been amended to delete the recitations of "SEQ ID NOS:67-811" and to incorporate the recitations of claim 34. Claim 32 also has been amended to recite the names of the open reading frames identified by each of the recited SAGE tags. Table 3, which associates the sequence identifier (SEQ ID NO) of each of the recited SAGE tags with a not previously assigned open reading frame (NORF) gene, supports this amendment.

Claim 32 has also been amended to recite "*Saccharomyces cerevisiae* genome" in place of "*Saccharomyces cerevisiae*" and "*Saccharomyces genome*." (Lines 3-4.) This amendment merely provides proper antecedent basis for this element and corrects a formatting error. It does not narrow the scope of claim 32.

Claim 43 has been amended to conform to the amendments to claim 32, on which it

depends. Claims 33 and 34 have been canceled as redundant.

None of these amendments introduces new matter or requires a new search.

The Rejection of Claims 32-37, 43, and 44 Under 35 U.S.C. § 101

Claims 32-37, 43, and 44 are rejected under 35 U.S.C. § 101 as lacking a patentable utility. Claims 33 and 34 have been canceled, mooting their rejection. Applicants respectfully traverse the rejection of claims 32, 35-37, 43, and 44.

The Office Action asserts two specific reasons why the claims lack patentable utility. First, the Office Action asserts that “the application does not disclose that each of the NORFs identified by the SAGE tags mentioned in the claims is indeed differentially expressed during the cell cycle.” (Paper 18, page 2 lines 10-11.) To advance prosecution, independent claim 32 has been amended to recite eight particular open reading frames (ORFs), *i.e.*, NORFs 1, 2, 4, 5, 6, 17, 25, and 27. The specification explicitly teaches that these NORFs are differentially expressed: “Genes which have been found to have differential expression characteristics include: NORF N^o 1, 2, 4, 5, 6, 17, 25, 27. . . .” (Page 6, line 31.) Thus, amended claim 32 recites NORFs that are disclosed as differentially expressed during the cell cycle.

Second, the Office Action asserts that the claims lack patentable utility because “it does not necessarily follow that each of the 14-mers contained in each of the so-identified NORFs is found only in DNAs that are differentially expressed during the cell cycle.” (Paper 18, page 2, lines 14-16.) A nucleotide sequence to which a probe having 14 contiguous nucleotides will hybridize should occur randomly once in every 4^{14} or 2.7×10^8 bases of DNA. This is because the probability of detecting a particular nucleotide at each position is 1 in 4 and there are 14

positions in the probe. The yeast genome, in contrast, has only approximately 12,068 kilobases or 1.2×10^7 bases. (See Goffeau cited in the rejection under 35 U.S.C. § 103 (a), Abstract, line 2.) It is therefore highly unlikely that a probe comprising at least 14 contiguous nucleotides would hybridize to more than one ORF in the *S. cerevisiae* genome since such sequences are not predicted to occur more than once in the genome. The Office Action merely speculates that each probe may not necessarily be found in DNA that is differentially expressed during the cell cycle. This speculation is not supported by the mathematical calculations. Rather, each of the recited probes should be found only in the corresponding recited NORF, each of which is differentially expressed during the cell cycle.

Withdrawal of this rejection to claims 32, 35-37, 43, and 44 is respectfully requested.

The Rejection of Claims 32-37, 43, and 44 Under 35 U.S.C. § 112, second paragraph

Claims 32-37, 43, and 44 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Claims 33 and 34 have been canceled, mooted their rejection. Applicants respectfully traverse to claims 32, 35-37, 43, and 44.

The Office Action asserts that the recitation of "wherein the open reading frame is identified by a SAGE tag" is unclear because the claims do not point out which ORFs are identified by the recited SAGE tags. (Paper 18, page 2, lines 20-22.) Claim 32, the independent claim of the rejected set, has been amended to specify the ORF identified by each of the recited SAGE tags. Thus the allegedly indefinite phrase has been clarified. Withdrawal of this rejection to claims 32, 35-37, 43, and 44 is respectfully requested.

The Rejection of Claims 32-37, 43, and 44 Under 35 U.S.C. § 103(a)

Claims 32-37, 43, and 44 are rejected under 35 U.S.C. § 103(a) as obvious over Goffeau *et al.* (*Science* 270, 546, October 25, 1996; "Goffeau") in view of Velculescu *et al.* (*Science* 274, 484, October 20, 1995; "Velculescu"). The Office Action relies on reasons of record set forth in Paper Nos. 7 (mailed January 10, 2001) and 11 (mailed June 11, 2001). Claims 33 and 34 have been canceled, mooting their rejection. Applicants respectfully traverse the rejection of claims 32, 35-37, 43, and 44.

Claim 32, the independent claim of the rejected claim set, recites a probe that comprises "at least 14 contiguous nucleotides of an open reading frame of a *Saccharomyces cerevisiae* genome . . . wherein the open reading frame is selected from the group consisting of the open reading frames identified by the SAGE tags shown in SEQ ID NO:67 (NORF 1), SEQ ID NO:68 (NORF 2), SEQ ID NO: 70 (NORF 4), SEQ ID NO: 71 (NORF 5), SEQ ID NO: 72 (NORF 6), SEQ ID NO: 83 (NORF 17), SEQ ID NO:91 (NORF 25), and SEQ ID NO:93 (NORF 27)"

To reject claims as *prima facie* obvious, the Patent Office must meet three criteria:

First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally the prior art reference (or references when combined) must teach or suggest all the claim limitations.

See MPEP § 2142. This rejection fails to meet the first criterion. Thus the *prima facie* case of obvious must fail.

Goffeau has been cited as teaching "the fact that the entire genome of *Saccharomyces cerevisiae* is known." (Paper 7, page 7, lines 7-8.) Velculescu has been cited as teaching "the

analysis of DNA by attaching DNA probes to a solid support.” (Paper 7, page 7, lines 8-9.) The current Office Action asserts that “the broad motivation of analysis of *Saccharomyces* DNA is sufficient to establish obviousness under 35 U.S.C, § 103(a).” (Paper 18, page 3, lines 5-6.)

On the contrary, this broad motivation, “to analyze” *S. cerevisiae* nucleic acid sequences, would have been insufficient to motivate one of ordinary skill in the art to combine the teachings of Goffeau and Velculescu and arrive at the claimed invention. One of skill in the art does not “analyze” in a vacuum. One of skill in the art analyzes for a reason. No reason exists in the prior art that would have motivated one of ordinary skill in the art to make the claimed array.

There are a limited number of reasons for analyzing nucleic acids: nucleic acids can be analyzed to determine their nucleotide sequence, their expression levels, their expression in different tissues, or for what they encode. Of course, because Goffeau discloses the entire nucleotide sequence of the *S. cerevisiae* genome, there would have been no motivation to determine the sequence again.

This leaves as possibilities for analysis either determination of levels or patterns of gene expression in tissues or identification of the encoded products. As to identification of encoded products, Applicants acknowledge that Goffeau teaches that “one of the major problems to be tackled during the next stage of the yeast genome project is to elucidate the biological functions of all these genes.” (Page 546, lines 6-9 of the Abstract.) Because the biological function of any gene is to encode a protein, Goffeau’s statement must be read to mean “elucidate the biological function of the encoded protein of all these genes.” This statement, however, would not have provided any motivation to attach the recited probes to a solid support in an array. Before this application was filed, none of the NORFs identified by the recited probes were known to be

expressed genes. The open reading frames, which Applicants refer to as "NORFs," ("not previously assigned open reading frames," page 6, line 20) are disclosed only in the present specification, not in the cited prior art. Thus, neither Goffeau nor Velculescu could possibly have provided any teaching or suggestion that would have motivated one of ordinary skill in the art to identify their expressed products. The NORFs identified by the recited probes were simply not known to be expressed genes.

The only "analysis" remaining and, indeed, the only purpose for which one of ordinary skill in the art would have attached probes to a solid support in an array, is to analyze expression patterns in tissues or levels of gene expression by hybridizing mRNA to the probes. Without any teaching in either Goffeau or Velculescu that the recited NORFs are expressed, however, there would have been no reason to attach the recited probes to a solid support in an array to detect gene expression. Without this teaching --present only in Applicants' specification-- such an array would have had no utility whatsoever and no ordinary artisan would have been motivated to make it.

The final Office Action dated June 11, 2001 asserts that because the claims recite that the probes comprise at least 14 contiguous nucleotides of a NORF gene, "there is no need for the references to disclose any of the ORFs mentioned in the application." (Paper 11, page 3, lines 8-9.) That is, the Office asserts that one of ordinary skill in the art would have been motivated to use a probe long enough to encompass nucleotides both of a known expressed gene to be analyzed and of a region of the *S. cerevisiae* genome not thought to expressed (*i.e.*, the 14 contiguous nucleotides of the NORF and all intervening sequences between the NORF and the known gene). This, however, is not true. One of ordinary skill in the art would not have been

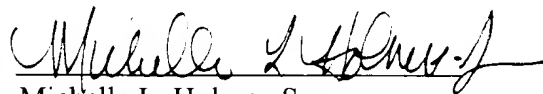
motivated to use such a probe to detect gene expression. On the contrary, to minimize non-specific hybridization, one of ordinary skill in the art would have been motivated to use a probe that hybridizes only to the nucleotide sequence of the known gene.

There simply is no teaching in the cited references or in the patent application sufficient to have motivated one of ordinary skill to have attached the recited probes to a solid support in an array.

Withdrawal of this rejection to claims 32-37, 43, and 44 is respectfully requested.

Respectfully submitted,

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Appendix I. Marked Up Version of the Claims to Show the Changes Made

32. (Three Times Amended) An array of probes on a solid support for detecting gene expression, wherein at least one probe comprises at least 14 contiguous nucleotides of an open reading frame of a *Saccharomyces cerevisiae* genome, wherein the *Saccharomyces cerevisiae* [*genome*] genome is shown in SEQ ID NOS:12,204-12,219, wherein the open reading frame is [identified by a SAGE tag as shown in SEQ ID NOS:67-811] selected from the group consisting of the open reading frames identified by the SAGE tags shown in SEQ ID NO:67 (NORF 1), SEQ ID NO:68 (NORF 2), SEQ ID NO: 70 (NORF 4), SEQ ID NO: 71 (NORF 5), SEQ ID NO: 72 (NORF 6), SEQ ID NO: 83 (NORF 17), SEQ ID NO:91 (NORF 25), and SEQ ID NO:93 (NORF 27).

43. (Twice Amended) The array of claim 32 which comprises at least one probe comprising at least 14 contiguous nucleotides of each of the open reading frames identified by the SAGE tags shown in SEQ ID NOS:[67-811] 67, 68, 70, 71, 72, 83, 91, and 93.